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Application of diethyl ethynylphosphonate to the synthesis of 3-phosphonylated β-lactams via the Kinugasa reaction[1]

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Dedicated to Prof. Jacek Młochowski on the occasion of his 80th birthday

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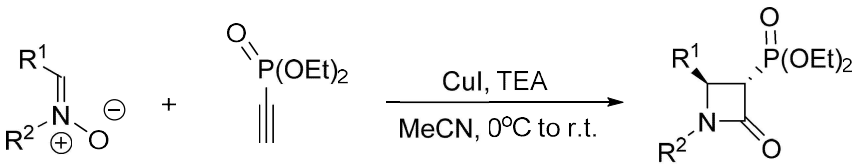
Abstract

The easily available diethyl ethynylphosphonate reacts with diverse aldonitrones under Kinugasa reaction conditions at room temperature, providing 3-phosphonylated β-lactams in good yields. In all cases, the reaction led to the *trans*-isomer exclusively. The *trans*-configuration was assigned based on ^{1}H-NMR spectroscopic analysis.

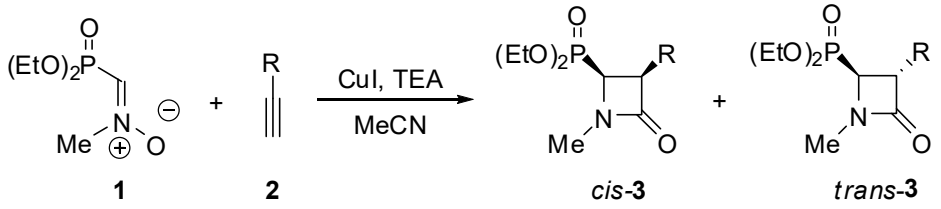


Keywords: β-Lactams, Kinugasa reaction, aldonitrones, ethynylphosphonate, cycloaddition reactions, copper(I) catalysis

Introduction

The importance of modified β-lactams is well documented. They are known not only as important drugs with antimicrobial activity[2] but also as inhibitors of cholesterol absorption[3] and thrombin,[4] as well as antitumor[5] and anti-HIV agents.[6] One of the important modifications comprises the substitution with phosphonyl groups, which are known as bioisosteric functionalities of phosphates.[7,8] The phosphonyl group can be located either at C(3) or C(4) of the β-lactam ring.

There are different methods known for the preparation of 4-phosphonylated β-lactams,[9–11] including the recently reported Kinugasa approach.[12] In the latter case, the *C*-phosphonylated *N*-methyl nitrone **1** was reacted with mono-substituted acetylenes **2** yielding azetidin-2-ones **3** as mixtures of *cis*/*trans*-isomers (Scheme 1).



1 **2**

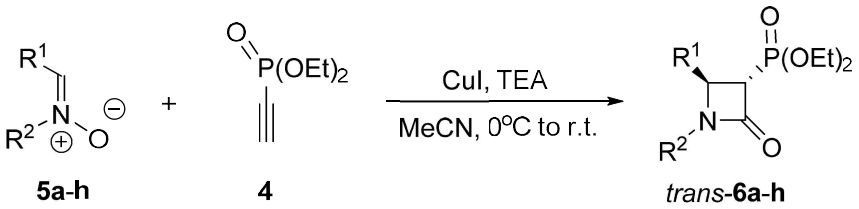
Scheme 1. Kinugasa reaction with a phosphonylated nitrone leading to 4-phosphonylated β-lactams.[12]

The synthesis of 3-phosphonylated β-lactams can be performed using different methods, *e.g.*, [2+2]-cycloaddition of a phosphonylated ketene with an imine (Staudinger reaction),[13,14] intramolecular carbene insertion into a CH-bond of an *N*-benzylamide,[15] and cyclization of phosphono acet-enamides.[16]

3-Phosphonylated β-lactams have never been prepared via Kinugasa reactions starting with diethyl ethynylphosphonate (**4**). Compound **4** has however been used extensively in [3+2]-cycloadditions with organic azides.[17–20]

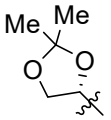
Results and Discussion

In a recent publication we described a new approach to the synthesis of fluorinated β-lactams via Kinugasa reactions with fluorinated nitrones and diverse monosubstituted acetylenes, including methyl propiolate.[21] In the course of that study, preliminary experiments with diethyl ethynylphosphonate (**4**) were unsuccessful and the formation of a complicated mixture of unidentified products was observed. For that reason, a series of typical nitrones **5a**-**h**, derived from aryl or alkyl aldehydes, was prepared and subsequently used for reaction with **4**. The first experiment with *N*-benzyl-*C*-phenyl nitrone (**5a**) and **4** was performed in anhydrous acetonitrile, in the presence of CuI and triethylamine (TEA), under an argon atmosphere, and after three days the expected diethyl 1-benzyl-2-oxo-4-phenylazetidine-3-phosphonate (**6a**) was obtained as a yellowish oil in 60% yield (Scheme 2). ^{1}H-NMR analysis of the crude product revealed the presence of a single product, which was identified as the *trans*-isomer on the basis of the HC(3)-HC(4) coupling constant of 2.1 Hz.[22] Analogously, β-lactams *trans*-**6b–h** with a benzyl, phenyl or methyl group at N(1) were obtained with complete diastereoselectivity and in good yields (Table 1). The type of substituent on the N-atom influences neither the reaction course nor the yield of the formed product.



Scheme 2. Kinugasa reaction with diethyl ethynylphosphonate (**4**) and nitrones **5.**

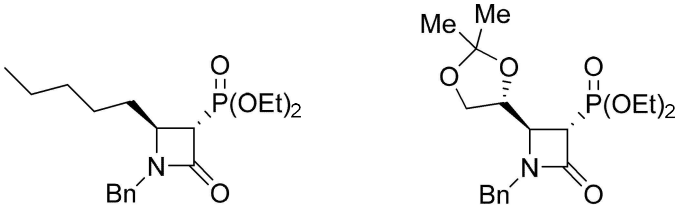
Table 1. β-Lactams **6** prepared via Kinugasa reaction with diethyl ethynylphosphonate (**4**)

Nitrone **5**	R^1	R^2	β-lactam **6**	Yield (%)[a]
a	Ph	$PhCH_2$	**a**	60
b	4-$MeOC_6H_4$	$PhCH_2$	**b**	61
c	4-$F_3CC_6H_4$	$PhCH_2$	**c**	32
d	4-BrC_6H_4	$PhCH_2$	**d**	56
e	furan-2-yl	$PhCH_2$	**e**	55
f	Ph	Ph	**f**	56
g	Ph	Me	**g**	60
h	4-MeC_6H_4	Me	**h**	62
i	$Me(CH_2)_4$	$PhCH_2$	**i**	26[b]
j		$PhCH_2$	**j**	58

[a] Yield of isolated product. [b] Contains ca. 5% of an unknown impurity.

In all reactions *trans*-isomers were isolated exclusively. It seems likely that initially formed *cis*-products undergo spontaneous isomerization under the basic reaction conditions and the thermodynamically more stable *trans*-isomers are formed as the final products. This explanation is the more likely as the H-C(3) is expected to show enhanced acidity resulting from the presence of the electron-withdrawing carbonyl and phosphonyl groups. In the case of the previously reported 4-phosphonylated β-lactams, the formation of mixtures in favor of the *trans*-isomers was observed (up to 78:22).[12]

In order to check the scope of the reaction, two nitrones derived from hexanal and (*S*)-glyceraldehyde acetonide, respectively, were included in the study of the reaction with **4**. In the case of **5i**, the *trans*-β-lactam **6i** was isolated in rather low yield (Figure 1, Table 1). However, again only one isomer was formed in this reaction. The reaction of the enantiopure **5j** with **4** gave only one optically active product, *trans*-**6j**, isolated in 58% yield. However, the absolute configuration at C(3) and C(4) in this compound remains unknown.



trans-**6i** (*R*)-*trans*-**6j**

Figure 1. β-Lactams *trans*-**6i** (racemic) and (*R*)-*trans*-**6j** (optically active)

Conclusions

The present study shows that 3-phosphonylated β-lactams can be prepared conveniently using easily available diethyl ethynylphosphonate as the acetylenic component in the Kinugasa reaction. In contrast to the alternative method with phosphonylated nitrones leading to 4-phosphonylated analogues,[12] the reaction occured with complete diastereoselectivity, and the *trans*-configurations were established in all cases based on the HC(3),HC(4) coupling constants in the ^{1}H-NMR spectra.[22]

Experimental Section

General. Melting points were determined in capillaries using a Stuart SMP30 apparatus and are uncorrected. IR spectra were recorded with a FT-IR NEXUS spectrophotometer as films or KBr pellets; absorptions in cm^{-1} (w = weak, m = medium, s = strong, vs = very strong). ^{1}H,^{13}C{^{1}H}, ^{31}P{^{1}H} and ^{19}F NMR spectra were measured on a Bruker Avance III instrument (^{1}H at 600, ^{13}C at 150, ^{31}P at 234, and ^{19}F at 565 MHz, respectively) in $CDCl_3$; chemical shifts (δ) are given in ppm, coupling constants (*J*) in Hz. The multiplicity of the ^{13}C signals was deduced using HMQC and HMBC techniques. ^{1}H NMR data are presented as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, dd = doublet of doublets, t = triplet, dt = doublet of triplets, q = quartet, m = multiplet), coupling constant, integration. The mass spectra were recorded on a Finnigan MAT-95 instrument (ESI). Elemental analyses were performed in the Microanalytical Laboratory of the Faculty of Chemistry of the University of Łódź. The applied reagent diethyl ethynylphosphonate (**4**) was prepared according to a slightly modified protocol described in ref. 25; the modification comprises the desilylation of the final product by using commercial tetrabutylammonium fluoride (TBAF) solution in THF. All nitrones **5a–j** were prepared from the corresponding aldehydes and *N*-hydroxyamines following the standard protocol.[26] Copper(I) iodide was purchased from Sigma-Aldrich. Anhydrous acetonitrile was purchased from Acros and was degassed before use. Triethylamine (TEA) was purchased from Avantor; it was dried by heating over solid KOH and freshly distilled prior to use.

Reaction of nitrones 5a–j with diethyl ethynylphosphonate (4). General Procedure

In an oven-dried flask equipped with a septum, stirring bar and a balloon filled with argon was placed copper(I) iodide (190 mg, 1.0 mmol). Anhydrous and degassed MeCN (2 mL) was introduced, and to the stirred suspension (ice bath), diethyl ethynylphosphonate (**4**, 162 mg, 1.0 mmol) dissolved in dry MeCN (2 mL) was

added. After 5 min a solution of Et_3N (202 mg, 2.0 mmol) in anhydrous and degassed MeCN (3 mL) was added at 0 °C (ice bath) while stirring under the inert atmosphere**.** After 10 min a solution of a nitrone **5a**–**j** (1.1 mmol) in dry MeCN (3 mL) was added to the suspension of the copper-acetylene complex. After another 10 min, the ice bath was removed and the reaction mixture was left at room temperature for 72 h. After this time, CH_2Cl_2 (5 mL) was added and the solvents were removed under reduced pressure. Crude products **6** were purified by flash column chromatography (conditions: Grace Reveleris X2 apparatus with UV-Vis and ELSD detection, using commercially available 12 g or 24 g SiO_2 columns, pressure 20 psi, solvent flow rate 25 mL/min) using petroleum ether with increasing amounts of EtOAc (up to 100%) as eluent.

Diethyl *trans*-1-benzyl-2-oxo-4-phenylazetidine-3-phosphonate (**6a**). Light-yellow oil (224 mg, 60%). IR (ν_{max}, cm^{-1}): 716m, 971w, 1025m, 1171w, 1260w, 1395w, 1450w, 1759s (C=O), 2854w, 2926w, 2986w. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.22 (3H, t, $^3J_{HH}$ 7.1 Hz, P(O)(OCH$_2$C*H$_3$*)$_2$), 1.23 (3H, t, $^3J_{HH}$ 7.1 Hz, P(O)(OCH$_2$C*H$_3$*)$_2$), 3.41 (1H, dd, $^3J_{HP}$ 14.8 Hz, $^3J_{HH}$ 2.1 Hz, C*H*P(O)(OCH$_2$CH$_3$)$_2$), 4.03–4.11 (4H, m, P(O)(OC*H$_2$*CH$_3$)$_2$), 3.76, 4.81 (2H, AB system, 2d, $^2J_{HH}$ 15.2 Hz, C*H$_2$*Ph), 4.55 (1H, dd, $^2J_{HP}$ 8.6 Hz, $^3J_{HH}$ 2.5 Hz, C*H*Ph), 7.12–7.13 (2H, m, 2CH$_{arom}$), 7.19–7.25 (5H, m, 5CH$_{arom}$), 7.26–7.31 (3H, m, 3CH$_{arom}$). ^{13}C NMR (150 MHz, $CDCl_3$) δ 16.3, 16.4 (2C, 2d, $^3J_{CP}$(1) 2.7 Hz, $^3J_{CP}$(2) 2.8 Hz, P(O)(OCH$_2$*C*H$_3$)$_2$), 45.0 (d, $^4J_{CP}$ 1.9 Hz, *C*H$_2$Ph), 55.3 (d, $^2J_{CP}$ 2.2 Hz, *C*HPh), 57.1 (d, $^1J_{CP}$ 143.3 Hz, *C*HP(O)(OCH$_2$CH$_3$)$_2$), 62.6, 62.7 (2C, 2d, $^2J_{CP}$(1) 6.2 Hz, $^2J_{CP}$(2) 6.4 Hz, P(O)(O*C*H$_2$CH$_3$)$_2$), 126.4, 127.8, 128.3, 128.7, 128.9, 129.1 (10CH$_{arom}$), 134.8 (1C$_{arom}$), 136.3 (d, $^3J_{CP}$ 2.3 Hz, 1C$_{arom}$), 161.4 (d, $^2J_{CP}$ 6.6 Hz, C=O). ^{31}P NMR (243 MHz, $CDCl_3$) δ 18.60 (s, *P*(O)(OCH$_2$CH$_3$)$_2$). MS: *m/z* (%) 396.3 (100, [*M*+Na]$^+$). Anal. Calcd for $C_{20}H_{24}NO_4P$ (373.38): C, 64.33; H, 6.48; N, 3.75. Found: C, 64.30; H, 6.44; N, 3.69%.

Diethyl *trans*-1-benzyl-4-(4-methoxyphenyl)-2-oxoazetidine-3-phosphonate (**6b**). Light-yellow oil (246 mg, 61%). IR (ν_{max}, cm^{-1}): 955m, 1032vs, 1167s, 1252vs, 1600s, 1763vs (C=O), 2932w, 2982w. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.31 (3H, t, $^3J_{HH}$ 7.1 Hz, P(O)(OCH$_2$C*H$_3$*)$_2$), 1.32 (3H, t, $^3J_{HH}$ 7.1 Hz, P(O)(OCH$_2$C*H$_3$*)$_2$), 3.49 (1H, dd, $^3J_{HP}$ 14.7 Hz, $^3J_{HH}$ 2.3 Hz, C*H*P(O)(OCH$_2$CH$_3$)$_2$), 3.80, 4.87 (2H, AB system, $^2J_{HH}$ 15.2 Hz, C*H$_2$*Ph), 3.83 (3H, s, OCH$_3$), 4.12–4.23 (4H, m, P(O)(OC*H$_2$*CH$_3$)$_2$), 4.60 (1H, dd, $^3J_{HP}$ 8.5 Hz, $^2J_{HH}$ 2.5 Hz, C*H*C$_6$H$_4$OCH$_3$), 7.19–7.22 (4H, m, 4CH$_{arom}$), 7.38–7.44 (1H, m, 1CH$_{arom}$), 7.27–7.34 (4H, m, 4CH$_{arom}$). ^{13}C NMR (150 MHz, $CDCl_3$): δ 16.3, 16.4 (2C, 2d, $^3J_{CP}$(1) 2.6 Hz, $^3J_{CP}$(2) 2.7 Hz, P(O)(OCH$_2$*C*H$_3$*)$_2$), 44.8 (d, $^4J_{CP}$ 1.8 Hz, *C*H$_2$Ph), 55.3 (d, $^2J_{CP}$ 2.8 Hz, *C*HC$_6$H$_4$OCH$_3$), 57.1 (d, $^1J_{CP}$ 142.7 Hz, *C*HP(O)(OCH$_2$CH$_3$)$_2$), 62.5, 62.6 (2C, 2d, $^2J_{CP}$(1) 6.2 Hz, $^2J_{CP}$(2) 6.4 Hz, P(O)(O*C*H$_2$CH$_3$)$_2$), 114.6 (OCH$_3$), 127.7, 127.8, 128.3, 128.7, 128.9, 129.2, 130.6 (9CH$_{arom}$), 134.9 (brs, 1C$_{arom}$), 160.1 (1C$_{arom}$), 161.1 (1C$_{arom}$), 162.0 (d, $^2J_{CP}$ 6.6 Hz, C=O). ^{31}P NMR (243 MHz, $CDCl_3$): δ 18.77 (s, P(O)(OCH$_2$CH$_3$)$_2$). MS: *m/z* (%) 426.3 (100, [*M*+Na]$^+$). Anal. Calcd for $C_{21}H_{26}NO_5P$ (403.41): C, 62.52; H, 6.50; N, 3.47. Found: C, 62.31; H, 6.33; N, 3.56%.

Diethyl *trans*-1-benzyl-2-oxo-4-[4-(trifluoromethyl)phenyl]azetidine-3-phosphonate (**6c**). Light-yellow oil (141 mg, 32%). IR (ν_{max}, cm^{-1}): 960s, 1117s, 1170s, 1255s, 1396m, 1600s, 1760vs (C=O), 2930m, 2982m. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.24 (6H, brt, $^3J_{HH}$ 7.0 Hz, P(O)(OCH$_2$C*H$_3$*)$_2$), 3.38 (1H, dd, $^3J_{HH}$ 14.9 Hz, $^3J_{HH}$ 2.2 Hz, C*H*C$_6$H$_4$CF$_3$), 4.01–4.13 (4H, m, P(O)(OC*H$_2$*CH$_3$)$_2$), 3.81, 4.81 (2H, AB system, $^2J_{HH}$ 15.2 Hz, C*H$_2$*Ph), 4.60 (1H, dd, $^3J_{HP}$ 8.7 Hz, $^2J_{HH}$ 2.6 Hz, C*H*P(O)(OCH$_2$CH$_3$)$_2$), 7.11–7.13 (2H, m, 2CH$_{arom}$), 7.20–7.25 (3H, m, 3CH$_{arom}$), 7.30–7.32 (2H, m, 2CH$_{arom}$), 7.55–7.56 (2H, m, 2CH$_{arom}$). ^{13}C NMR (150 MHz, $CDCl_3$): δ 16.3, 16.4 (2C, 2d, $^3J_{CP}$(1) 1.8 Hz, $^3J_{CP}$(2) 2.0 Hz, P(O)(OCH$_2$*C*H$_3$*)$_2$), 45.4 (d, $^4J_{CP}$ 1.8 Hz, *C*H$_2$Ph), 54.7 (d, $^2J_{CP}$ 2.0 Hz, *C*HC$_6$H$_4$CF$_3$), 57.2 (d, $^1J_{CP}$ 143.9 Hz, *C*HP(O)(OCH$_2$CH$_3$)$_2$), 62.8, 62.9 (2C, 2d, $^2J_{CP}$(1) 6.2 Hz, $^2J_{CP}$(2) 6.5 Hz, P(O)(O*C*H$_2$CH$_3$)$_2$), 123.8 (q, $^1J_{CF}$ 270.6 Hz, CF$_3$), 126.1 (q, $^3J_{CF}$ 37.2 Hz, 2 CH$_{arom}$), 128.0 (1C$_{arom}$), 126.8, 128.4, 128.8 (5CH$_{arom}$), 131.2 (q, $^2J_{CF}$ 32.6 Hz, *C*$_{arom}$CF$_3$), 134.4 (1C$_{arom}$), 140.7 (brs, 1C$_{arom}$), 161.6 (d, $^2J_{CP}$ 6.5 Hz, C=O). ^{31}P NMR (243 MHz, $CDCl_3$): δ 18.60 (s,

P(O)(OCH_2CH_3)$_2$). ^{19}F NMR (565 MHz, $CDCl_3$): δ –62.78 (s, CF_3). MS: *m/z* (%) 464.2 (100, [*M*+Na]$^+$). Anal. Calcd for $C_{21}H_{26}NO_5P$ (441.38): C, 57.14; H, 5.25; N, 3.17. Found: C, 57.30; H, 5.41; N, 3.10%.

Diethyl *trans*-1-benzyl-4-(4-bromophenyl)-2-oxoazetidine-3-phosphonate (**6d**). Light-yellow oil (253 mg, 56%). IR (ν$_{max}$, cm^{-1}): 732w, 884m, 970m, 1027s, 1154m, 1249m, 1394s, 1486m, 1765vs (C=O), 2933m, 3028w. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.22, 1.23 (6H, 2t, $^3J_{HH}$(1) 7.0 Hz, $^3J_{HH}$(2) 7.1 Hz, P(O)(OCH_2CH_3)$_2$), 3.36 (1H, dd, $^3J_{HP}$ 14.8 Hz, $^3J_{HH}$ 2.0 Hz, C*H*P(O)(OCH_2CH_3)$_2$), 4.02–4.12 (4H, m, P(O)(OCH_2CH_3)$_2$), 3.76, 4.78 (2H, AB system, $^2J_{HH}$ 15.2 Hz, CH_2Ph), 4.50 (1H, dd, $^3J_{HP}$ 8.7 Hz, $^2J_{HH}$ 2.6 Hz, C*H*$C_6H_4OCH_3$), 7.05–7.06 (1H, m, 1CH$_{arom}$), 7.10–7.12 (2H, m, 2CH$_{arom}$), 7.19–7.25 (4H, m, 4CH$_{arom}$), 7.41–7.43 (2H, m, 2CH$_{arom}$). ^{13}C NMR (150 MHz, $CDCl_3$): δ 16.3, 16.4 (2C, 2d, $^3J_{CP}$(1) 2.1 Hz, $^3J_{CP}$(2) 2.3 Hz, P(O)(OCH_2CH_3)$_2$), 45.1 (d, $^4J_{CP}$ 1.9 Hz, *C*H$_2$Ph), 54.7 (d, $^2J_{CP}$ 2.1 Hz, *C*HC_6H_4Br), 57.1 (d, $^1J_{CP}$ 143.5 Hz, *C*HP(O)(OCH_2CH_3)$_2$), 62.7, 62.8 (2d, $^2J_{CP}$(1) 6.2 Hz, $^2J_{CP}$(2) 6.4 Hz, P(O)(OCH_2CH_3)$_2$), 127.9, 128.1, 128.4, 128.8, 132.4 (9CH$_{arom}$), 122.9, 134.5 (2C$_{arom}$), 135.5 (d, $^3J_{CP}$ 2.4 Hz, 1C$_{arom}$), 161.7 (d, $^2J_{CP}$ 6.6 Hz, C=O). ^{31}P NMR (243 MHz, $CDCl_3$): δ 18.19 *(s*, P(O)(OCH_2CH_3)$_2$). MS: *m/z* (%) 474.2, 476.2 (100, 65 [*M*+Na]$^+$). Anal. Calcd for $C_{21}H_{26}NO_5P$ (452.28): C, 53.11; H, 5.13; N, 3.10. Found: C, 53.16; H, 5.38; N, 3.32%.

Diethyl *trans*-1-benzyl-4-(furan-2-yl)-2-oxoazetidine-3-phosphonate (**6e**). Light-yellow oil (200 mg, 55%). IR (ν$_{max}$, cm^{-1}): 701s, 745vs, 970s, 1027vs, 1268vs, 1401s, 1774vs (C=O), 2908m, 2984s, 2985w, 3050m. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.33, 1.34 (6H, 2t, $^3J_{HH}$(1) 7.0 Hz, $^3J_{HH}$(2) 6.9 Hz, P(O)(OCH_2CH_3)$_2$), 3.87 (1H, dd, $^3J_{HH}$ 11.8 Hz, $^3J_{HP}$ 2.6 Hz, C(4)H), 3.91, 4.74 (2H, AB system, $^2J_{HH}$ 5.3 Hz, CH_2Ph), 4.16–4.24 (4H, m, P(O)(OCH_2CH_3)$_2$), 4.69 (1H, dd, $^3J_{HH}$ 6.1 Hz, $^2J_{HP}$ 2.6 Hz, C*H*P(O)(OCH_2CH_3)$_2$), 6.31–6.32 (1H, m, 1CH$_{arom}$), 6.34–6.35 (1H, m, 1CH$_{arom}$), 7.23–7.24 (2H, m, 2CH$_{arom}$), 7.27–7.30 (1H, m, 1CH$_{arom}$), 7.32–7.34 (2H, m, 2CH$_{arom}$), 7.40–7.41 (1H, m, 1CH$_{arom}$). ^{13}C NMR (150 MHz, $CDCl_3$): δ 16.3, 16.4 (2C, 2d, $^3J_{CP}$(1) 3.4 Hz, $^3J_{CP}$(2) 4.0 Hz, P(O)(OCH_2CH_3)$_2$), 45.2 (d, $^4J_{CP}$ 1.5 Hz, *C*H$_2$Ph), 48.7 (d, $^2J_{CP}$ 2.1 Hz, C(4)H), 53.5 (d, $^1J_{CP}$ 144.3 Hz, *C*HP(O)(OCH_2CH_3)$_2$), 62.7, 62.8 (2C, 2d, $^2J_{CP}$(1) 6.2 Hz, $^2J_{CP}$(2) 6.4 Hz, P(O)(OCH_2CH_3)$_2$), 110.5, 110.6, 127.7, 128.2, 128.7 (8CH$_{arom}$), 143.5 (1CH$_{arom}$), 134.9 (1C$_{arom}$), 148.6 (d, $^3J_{CP}$ 2.9 Hz, 1C$_{arom}$), 161.5 (d, $^2J_{CP}$ 6.6 Hz, C=O). ^{31}P NMR (243 MHz, $CDCl_3$): δ 18.44 (s, *P*(O)(OCH_2CH_3)$_2$). MS: *m/z* (%) = 386.2 (100, [*M*+Na]$^+$). Anal. Calcd for $C_{18}H_{22}NO_5P$ (363.34): C, 59.50; H; 6.10; N, 3.85. Found: C, 59.53; H, 6.04; N, 3.56%.

Diethyl *trans*-2-oxo-1,4-diphenylazetidine-3-phosphonate (**6f**)**.** Pale orange crystals (201 mg, 56%), mp 93–95 ^{o}C (CH_2Cl_2/petroleum ether). IR (ν$_{max}$, cm^{-1}): 690m, 777s, 981s, 1045s, 1149m, 1270s, 1385s, 1505s, 1600m, 1699w, 1746vs (C=O), 2849w, 2963m, 2981m, 3063w. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.18–1.17 (6H, m, P(O)(OCH_2CH_3)$_2$), 3.47 (1H, dd, $^3J_{HP}$ 15.5 Hz, $^3J_{HH}$ 2.8 Hz, C*H*P(O)(OCH_2CH_3)$_2$), 4.09–4.25 (4H, m, P(O)(OCH_2CH_3)$_2$), 5.15 (1H, dd, $^3J_{HP}$ 9.2 Hz, $^2J_{HH}$ 2.8 Hz, C*H*Ph), 7.26–7.30 (5H, m, 5CH$_{arom}$), 7.15–7.21 (5H, m, 5CH$_{arom}$). ^{13}C NMR (150 MHz, $CDCl_3$): δ 16.4 (d, $^3J_{CP}$ 2.7 Hz, P(O)(OCH_2CH_3)$_2$), 55.9 (d, $^2J_{CP}$ 2.3 Hz, *C*HPh), 57.3 (d, $^1J_{CP}$ 143.3 Hz, *C*HP(O)(OCH_2CH_3)$_2$), 62.8, 63.2 (2C, 2d, $^2J_{CP}$(1) 6.5 Hz, $^2J_{CP}$(2) 6.2 Hz, P(O)(OCH_2CH_3)$_2$), 117.0, 124.3, 125.9, 128.9, 129.1, 129.3 (10CH$_{arom}$), 136.6 (d, $^3J_{CP}$ 2.6 Hz, 1C$_{arom}$), 137.3 (d, $^4J_{CP}$ 2.1 Hz, 1C$_{arom}$), 159.0 (d, $^2J_{CP}$ 6.3 Hz, C=O). ^{31}P NMR (243 MHz, $CDCl_3$): δ 17.97 (s, *P*(O)(OCH_2CH_3)$_2$). MS: *m/z* (%) 382.3 (100, [*M*+Na]$^+$). Anal. Calcd for $C_{19}H_{22}NO_4P$ (359.36): C, 63.50; H, 6.17; N, 3.90. Found C, 63.76; H, 6.10; N, 3.92%.

Diethyl *trans*-1-methyl-2-oxo-4-phenylazetidine-3-phosphonate (**6g**). Light-yellow oil (178 mg, 60%). IR (ν$_{max}$, cm^{-1}): 824m, 1028m, 1052s, 1166m, 1252s, 1442m, 1453w, 1761vs (C=O), 2927m, 2984m. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.33 (3H, t, $^3J_{HH}$ 7.0 Hz, P(O)(OCH_2CH_3)$_2$), 1.38 (3H, t, $^3J_{HH}$ 7.0 Hz, P(O)(OCH_2CH_3)$_2$), 2.83 (3H, brs, NCH_3), 3.44 (1H, dd, $^2J_{HP}$ 16.5 Hz, $^3J_{HH}$ 1.6 Hz, C*H*P(O)(OCH_2CH_3)$_2$), 4.12–4.32 (4H, m, P(O)(OCH_2CH_3)$_2$), 4.73 (1H, dd, $^3J_{HP}$ 10.9 Hz, $^2J_{HH}$ 2.5 Hz, C*H*Ph), 7.32–7.33 (2H, m, 2CH$_{arom}$), 7.36–7.39 (1H, m, 1CH$_{arom}$), 7.41–7.43 (2H, m, 2CH$_{arom}$). ^{13}C NMR (150 MHz, $CDCl_3$): δ 16.3, 16.4 (2C, 2d, $^3J_{CP}$(1) 1.9 Hz, $^3J_{CP}$(2) 1.8 Hz, P(O)(OCH_2CH_3)$_2$), 27.6 (d,

$^4J_{CP}$ 1.6 Hz, NCH_3), 57.3 (d, $^2J_{CP}$ 2.5 Hz, *C*HPh), 57.6 (d, $^1J_{CP}$ 143.2 Hz, *C*HP(O)(OCH_2CH_3)$_2$), 62.5, 62.9 (2C, 2d, $^2J_{CP}$(1) 6.1 Hz, $^2J_{CP}$(2) 6.5 Hz, P(O)(OCH_2CH_3)$_2$), 126.2, 128.9, 129.2 ($5CH_{arom}$), 136.5 (d, $^3J_{CP}$ 2.4 Hz, $1C_{arom}$), 162.0 (d, $^2J_{CP}$ 6.2 Hz, C=O). ^{31}P NMR (243 MHz, $CDCl_3$): δ 18.96 (s, P(O)(OCH_2CH_3)$_2$). MS: *m/z* (%) 320.2 (100, [*M*+Na]$^+$). Anal. Calcd for $C_{14}H_{20}NO_4P$ (297.29): C, 56.56; H, 6.78; N, 4.71. Found: C, 56.75; H, 7.00; N, 4.43%.

Diethyl *trans*-1-methyl-4-(4-methylphenyl)-2-oxoazetidine-3-phosphonate (**6h**). Light-yellow oil (193 mg, 62%). IR (ν_{max}, cm^{-1}): 973s, 1014m, 1049s, 1160m, 1252s, 1388w, 1442m, 1511w, 1761vs (C=O), 2927m, 2984m. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.32 (3H, t, $^3J_{HH}$ 7.1 Hz, P(O)(OCH_2CH_3)$_2$), 1.36 (3H, t, $^3J_{HH}$ 7.0 Hz, P(O)(OCH_2CH_3)$_2$), 2.37 (s, 3H, $CH_3C_6H_4$), 2.80 (3H, s, NCH_3), 3.41 (1H, dd, $^2J_{HP}$ 16.4 Hz, $^3J_{HH}$ 1.6 Hz, *C*HP(O)(OCH_2CH_3)$_2$), 4.10–4.31 (4H, m, P(O)(OCH_2CH_3)$_2$), 4.68 (1H, dd, $^3J_{HP}$ 10.9 Hz, $^2J_{HH}$ 2.5 Hz, *C*H$C_6H_4CH_3$), 7.19–7.22 (4H, m, $4CH_{arom}$). ^{13}C NMR (150 MHz, $CDCl_3$): δ 16.3, 16.4 (2C, 2d, $^3J_{CP}$(1) 1.9 Hz, $^3J_{CP}$(2) 1.9 Hz, P(O)(OCH_2CH_3)$_2$), 27.5 (d, $^4J_{CP}$ 1.6 Hz, NCH_3), 21.1 ($CH_3C_6H_4$), 54.1 (d, $^2J_{CP}$ 2.8 Hz, *C*H$C_6H_4CH_3$), 57.6 (d, $^1J_{CP}$ 137.5 Hz, *C*HP(O)(OCH_2CH_3)$_2$), 62.4, 62.9 (2C, 2d, $^2J_{CP}$(1) 6.0 Hz, $^2J_{C,P}$(2) 6.4 Hz, P(O)(OCH_2CH_3)$_2$), 126.2, 129.8 ($4CH_{arom}$), 133.4 (d, $^3J_{CP}$ 2.4 Hz, $1C_{arom}$), 138.9 ($1C_{arom}$), 162.0 (d, $^2J_{CP}$ 6.2 Hz, C=O). ^{31}P NMR (243 MHz, $CDCl_3$): δ 19.11 (s, P(O)(OCH_2CH_3)$_2$). MS: *m/z* (%) 334.3 (100, [*M*+Na]$^+$). Anal. Calcd for $C_{15}H_{22}NO_4P$ (311.31): C, 57.87; H, 7.12; N, 4.50. Found: C, 57.65; H, 7.15; N, 4.51%.

Diethyl *trans*-1-benzyl-2-oxo-4-(pent-1-yl)azetidine-3-phosphonate (**6i**). Pale-yellow oil (96 mg, 26%); could not be obtained in analytically pure form (see Table 1). IR (ν_{max}, cm^{-1}): 731s, 1023s, 1241s, 1404m, 1457m, 1757vs (C=O), 2927s, 3053m. ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.87 (3H, t, $^2J_{HP}$ 15.0 Hz, CH_3), 1.20–1.47 (14H, m, P(O)(OCH_2CH_3)$_2$, (CH_2)$_4$), 3.26 (1H, dd, $^2J_{HP}$ 15.0 Hz, $^3J_{HH}$ 2.3 Hz, *C*HP(O)(OCH_2CH_3)$_2$), 3.69–3.73 (1H, m, *C*H(CH_2)$_4$), 4.12, 4.72, (2H, AB system, $^2J_{HH}$ 15.5 Hz, CH_2Ph), 4.16–4.24 (4H, m, P(O)(OCH_2CH_3)$_2$), 7.31–7.32 (3H, m, $3CH_{arom}$), 7.35–7.38 (2H, m, $2CH_{arom}$). ^{13}C NMR (150 MHz, $CDCl_3$): δ 16.4 (d, $^3J_{CP}$ 6.1 Hz, P(O)(OCH_2CH_3)$_2$), 32.6 (d, $^3J_{CP}$ 2.6 Hz, CHCH_2), 44.8 (d, $^4J_{CP}$ 1.9 Hz, CH_2Ph), 52.8 (d, $^1J_{CP}$ 145.9 Hz, *C*HP(O)(OCH_2CH_3)$_2$), 53.2 (d, $^2J_{CP}$ 2.7 Hz, *C*H(CH_2)$_4$), 62.4, 62.6 (2C, 2d, $^2J_{CP}$(1) 6.3 Hz, $^2J_{CP}$(2) 6.5 Hz, P(O)(OCH_2CH_3)$_2$), 127.7, 128.1, 128.7 ($5CH_{arom}$), 135.4 ($1C_{arom}$), 161.7 (d, $^2J_{CP}$ 6.6 Hz, C=O). ^{31}P NMR (243 MHz, $CDCl_3$): δ 20.00 (s, P(O)(OCH_2CH_3)$_2$). MS: *m/z* (%) 390.4 (100, [*M*+Na]$^+$).

Diethyl (*R*)-*trans*-1-benzyl-4-(2,2-dimethyl-1,3-dioxolan-4-yl)-2-oxoazetidine-3-phosphonate (**6j**). Pale-yellow oil (230 mg, 58%). $[\alpha]_D^{22}$ = +36.4 (c 1.0 in DCM). IR (ν_{max}, cm^{-1}): 970m, 1028m, 1042m, 1155m, 1257m, 1381w, 1453w, 1763vs (C=O), 2931w, 2985w. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.19–1.29 (6H, m, P(O)(OCH_2CH_3)$_2$), 1.25, 1.27 (6H, 2s, $2CH_3$), 3.20 (1H, dd, $^3J_{HP}$ 14.9 Hz, $^3J_{HH}$ 2.4 Hz, *C*HP(O)(OCH_2CH_3)$_2$)), 3.58 (1H, dt, $^3J_{HH}$(1) 6.6 Hz, $^3J_{HH}$(2) 2.7 Hz, C*H*OC(CH_3)$_2$), 3.69 (1H, dd, $^2J_{HH}$(1) 8.9 Hz, $^3J_{HH}$(2) 4.9 Hz, CH_2OC(CH_3)$_2$), 3.93 (1H dd, $^2J_{HH}$(1) 8.9 Hz, $^3J_{HH}$(2) 6.9 Hz, CH_2OC(CH_3)$_2$), 4.55 (1H, dd, $^3J_{HH}$ 6.1 Hz, $^2J_{HP}$ 2.5 Hz, *C*HP(O)(OCH_2CH_3)$_2$), 4.04–4.12 (5H, m, P(O)(OCH_2CH_3)$_2$), *C*HP(O)(OCH_2CH_3)$_2$), 4.12, 4.77 (2H, AB system, $^2J_{HH}$ 15.2 Hz, CH_2Ph), 7.20–7.21 (1H, m, $1CH_{arom}$), 7.26–7.27 (4H, m, $4CH_{arom}$). ^{13}C NMR (150 MHz, $CDCl_3$): δ 16.3, 16.4 (2C, 2d, $^3J_{CP}$(1) 4.2 Hz, $^3J_{C,P}$(2) 4.2 Hz, P(O)(OCH_2CH_3)$_2$), 25.0, 26.5 (C(CH_3)$_2$), 45.8 (d, $^4J_{CP}$ 1.9 Hz, CH_2Ph), 49.3 (d, $^1J_{CP}$ 147.8 Hz, *C*HP(O)(OCH_2CH_3)$_2$), 54.3 (d, $^2J_{CP}$ 1.9 Hz, *C*HCHP(O)(OCH_2CH_3)$_2$), 62.6, 62.7 (2C, 2d, $^2J_{C,P}$(1) 6.3 Hz, $^2J_{CP}$(2) 6.4 Hz, P(O)(OCH_2CH_3)$_2$), 66.0 (CH_2OC(CH_3)$_2$), 77.5 (d, $^2J_{CP}$ 3.5 Hz, *C*HCHP(O)(OCH_2CH_3)$_2$), 110.6 (*C*(CH_3)$_2$), 127.7, 128.6, 128.6 ($4CH_{arom}$), 135.4 ($1C_{arom}$), 161.1 (d, $^2J_{CP}$ 6.6 Hz, C=O). ^{31}P NMR (243 MHz, $CDCl_3$): δ 19.06 (s, P(O)(OCH_2CH_3)$_2$). MS: *m/z* (%) = 420.3 (100, [*M*+Na]$^+$). Anal. Calcd for $C_{19}H_{28}NO_6P$ (397.40): C, 57.42; H, 7.10; N, 3.52. Found: C, 57.40; H, 7.34; N, 3.33%.

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References

1. Part of the planned Ph.D. thesis of M. K. K., University of Łódź.
2. Arya, N.; Jagdale, A. Y.; Patil, T. A.; Yeramwar, S. S.; Holikatti, S. S.; Dwivedi, J.; Shishoo, C. J.; Jain, K. S. *Eur. J. Med. Chem*. **2014**, *74*, 619. http://dx.doi.org/10.1016/j.ejmech.2014.01.002
3. Burnett, D. A.; Caplen, M. A. Jr.; Davis, H. R.; Burrier, R. E.; Clader, J. W. *J. Med. Chem.* **1994**, *37*, 1733. http://dx.doi.org/10.1021/jm00038a001
4. Han, W. T.; Trehan, A. K.; Wright, J. J. K.; Federici, M. E.; Seiler, S. M.; Meanwell, N. A. *Bioorg. Med. Chem.* **1995**, *3*, 1123. http://dx.doi.org/10.1016/0968-0896(95)00101-L
5. Sun, L.; Vasilevich, N. I.; Fuselier, J. A.; Hocart, S. J.; Coy, D. H. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2041. http://dx.doi.org/10.1016/j.bmcl.2004.02.050
6. Sperka, T.; Pitlik, J.; Bagossia, P.; Tożsera, J. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3086. http://dx.doi.org/10.1016/j.bmcl.2005.04.020
7. Elliot, T.S.; Slowey, A.; Ye, Y.; Conway, S. J. *Med. Chem. Comm.* **2012**, *3*, 735. http://dx.doi.org/10.1039/c2md20079a
8. Rye, C.; Baell, J. *Curr. Med. Chem.* **2005**, *12*, 3127. http://dx.doi.org/10.2174/092986705774933452
9. Van Speybrock, V.; Moonen, K.; Hemelsoet, K.; Stevens, C. V.; Waroquier, M. *J. Am. Chem. Soc.* **2006**, *128*, 8468. http://dx.doi.org/10.1021/ja0584119
10. Moonen, K.; Stevens, C. V. *Synthesis* **2005**, 3603. http://dx.doi.org/10.1055/s-2005-918440
11. Shiozaki, M.; Masuko, H. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 645. http://dx.doi.org/10.1246/bcsj.60.645
12. Piotrowska, D. G.; Bujnowicz, A.; Wróblewski, A. E.; Głowacka, I. E. *Synlett* **2015**, *26*, 375. http://dx.doi.org/10.1055/s-0034-1379506
13. Nahmany, M.; Melman, A. *J. Org. Chem.* **2006**, *71*, 5804. http://dx.doi.org/10.1021/jo0607010
14. Qi, H.; Li, X.; Xu, J. *Org. Biomol. Chem.* **2011**, *9*, 2702. http://dx.doi.org/10.1039/C0OB00783H
15. Candeias, N. R.; Gois, P. M. P.; Afonso, C. A. M. *J. Org. Chem.* **2006**, *71*, 5489. http://dx.doi.org/10.1021/jo060397a
16. Punda, P.; Makowiec, S. *New J. Chem*. **2013**, *37*, 2254. http://dx.doi.org/10.1039/C3NJ00192J

17. Thiery, E.; You, V.; Mora, A.-S.; Abarbri, M. *Eur. J. Org. Chem*. **2016**, 529. http://dx.doi.org/10.1002/ejoc.201501266
18. Oakdale, J. S.; Sit, R. K.; Fokin, V. V. *Chem. Eur. J*. **2014**, *20*, 11101 http://dx.doi.org/10.1002/chem.201402559
19. Mukai, S.; Flematti, G. R.; Byrne, L. T.; Besant, P. G.; Attwood, P. V.; Piggott, M. J. *Amino Acids* **2012**, *43*, 857. http://dx.doi.org/10.1007/s00726-011-1145-2
20. McAllister, T. E.; Nix, M. G.; Webb, M. E. *Chem. Commun*. **2011**, *47*, 1297. http://dx.doi.org/10.1039/C0CC04238B
21. Kowalski, M. K.; Mlostoń, G.; Obijalska, E.; Linden, A.; Heimgartner, H. *Tetrahedron **2016**, in press.*
22. Tanaka, H.; Abdul Hai, A. K. M.; Sadakane, M.; Okumoto, H.; Torii, S. *J. Org. Chem*. **1994**, *59*, 3040. http://dx.doi.org/10.1021/jo00090a0
23. Santoro, S.; Liao, R-Z.; Marcelli, T.; Hammar, P.; Himo, F. *J. Org. Chem.* **2015**, *80*, 2649. http://dx.doi.org.10.1021/jo502838p
24. For a review on the Kinugasa reaction, see: Stecko, S.; Furman, B.; Chmielewski, M. *Tetrahedron* **2014**, *70*, 7817. http://dx.doi.org/10.1016/j.tet.2014.06.024
25. Vuilhorgne, M.; Malpart J.; Mutti S.; Mignani S. *J. Heterocycl. Chem*. **2003**, *40*, 159. http://dx.doi.org/10.1002/jhet.5570400122
26. Richmond, E.; Duguet, N.; Slawin, A. M. Z.; Lébl, T.; Smith A. D. *Org. Lett*. **2012**, *14*, 2762. http://dx.doi.org/10.1021/ol300982f

